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PENICILLIN-STREPTOMYCIN COMBINATIONS

If the number of parenteral penicillin-streptomycin preparations available to the physician is a reflection of their popularity, they are being seriously misused; there are few clear-cut indications for simultaneous treatment with the two antibiotics, and for these indications, the fixed-ratio combinations are likely to be either inadequately effective or hazardous. Among the penicillin-streptomycin combinations offered by the major pharmaceutical houses are Strep-Combiotic (Pfizer), Durycin (Lilly), Strep-Dicrysticin (Squibb), and Penicillin-Streptomycin Readimixed (Upjohn).

In all common coccal infections requiring antibacterial therapy, such as pneumonia, otitis media and pharyngitis, the proper dosage of a single antibiotic — penicillin or (in penicillin-allergic patients) erythromycin or one of the tetracycline group — gives results which cannot be improved by the addition of streptomycin. The most important indication for supplementing penicillin with streptomycin is bacterial endocarditis caused by either Streptococcus mitis (viridans) or Streptococcus faecalis (enterococcus). In these infections the combination is much more effective than penicillin alone.

USES OF COMBINATION - Streptomycin should always be used along with penicillin for endocarditis due to enterococci, or to viridans streptococci which are inhibited only by 0.2 units or more of penicillin per cc. In such cases, as much as 20,000,000 units of penicillin and 2 Gm. of streptomycin a day may be required for a period of two weeks, after which the dosage of streptomycin is reduced to 1 Gm. daily for an additional two weeks or more. Even when less than 0.2 units of penicillin per cc. is required for inhibition of viridans streptococci, the addition of streptomycin may shorten the course of therapy from about six weeks for penicillin alone to two weeks with the combination.

Most fixed-ratio penicillin-streptomycin combinations contain 0.5 Gm. of streptomycin to each 400,000 units of penicillin. Thus, it is obvious that when 4,000,000 units of penicillin daily are required for the treatment of a streptococcal endocarditis, such a combination would provide 5 Gm. of streptomycin — an excess of 3 Gm. If 10,000,000 units of penicillin were required, the total daily dose of streptomycin would be 12.5 Gm. These excesses of streptomycin markedly and unnecessarily increase the risk of vestibular nerve damage and of other toxic effects of the drug. According to a warning released by the Pfizer company,

in children or in debilitated or elderly adults more than 10 mg. of streptomycin per kilogram of body weight per day may cause severe respiratory and central-nervous-system depression.

INFECTIONS OF UNKNOWN CAUSE - Penicillin-streptomycin combinations are often used in home and office as well as in the hospital as an antibiotic blunderbuss to combat mixed infections or infections of unknown bacterial etiology. Generally, infections should not be treated with either single agents or combinations of antibiotics unless the patient is seriously ill or laboratory studies have disclosed the presence of threatening organisms. When bacterial infection is suspected in critically ill patients (as in acute meningitis of suspected bacterial origin, but showing no organisms on Gram, acid fast or India ink stains of the spinal fluid), treatment can be started with penicillin, and tetracycline or chloramphenicol added an hour later. The delay in the use of the broad-spectrum bacteriostatic drug minimizes the risk of antagonism. If the source of the infection (for example, the urinary tract) strongly suggests a gram-negative infecting organism, there need be no delay in administering the broad-spectrum antibiotic. Most uncomplicated urinary-tract infections are caused by gram-negative bacilli alone, and penicillin has little to contribute to treatment.

MIXED INFECTIONS - In mixed-infection peritonitis (as from a ruptured appendix), penicillin dosage is certain to be inadequate for the gram-positive cocci when the amount is restricted by the streptomycin content of fixed-ratio preparations. When several different organisms are involved in a serious infection, it is desirable to direct therapy against each specifically, on the basis of bacterial cultures and in vitro sensitivity tests. Therapy should not be delayed, however, and until the results of the tests are available the choice of a combination of drugs should be based on experience and clinical judgment. Thus, in fecal peritonitis, the streptococci and clostridia would require the use of penicillin, and the coliform and bacteroid organisms, streptomycin. But each antibiotic should be used in the doses which will insure maximum total effect. Fixed-ratio combinations of penicillin and streptomycin are likely to be either inadequate or hazardous for mixed infections requiring both agents.

For antibiotic prophylaxis of severe traumatic injuries, W. A. Altemeier and J. H. Wulsin (JAMA, 173:527, 1960) recommend penicillin alone — 250,000 to 500,000 units intramuscularly every six to eight hours for five days. If there is a compound fracture, about 1,000,000 units every three hours is recommended. Streptomycin in a dose of 0.5 Gm. at 12-hour intervals should supplement penicillin in traumatic perforations of the colon and urinary tract (D. V. Habif in Trauma, Saunders, 1959).

Fixed-ratio combinations of penicillin and streptomycin have been used to treat both mild and severe respiratory-tract infections, but such use is not supported by what is known of the etiology and clinical course of these infections. The commonest microorganisms responsible for severe bacterial respiratory infections are gram-positive, and will respond to penicillin or to erythromycin or its analogues; erythromycin is effective against many resistant staph strains. In respiratory infections by a gram-negative organism such as Hemophilus influenzae, a tetracycline can be used.

TOXIC EFFECTS OF STREPTOMYCIN IN COMBINATIONS - The occurrence of severe toxic respiratory and central-nervous-system depressive reactions in pediatric patients treated with penicillin-streptomycin combinations has resulted in a recent requirement by the Food and Drug Administration that manufacturers of such combinations include the following caution in the package insert: "Not for Pediatric Use." While such reactions have been noted mainly in children, as indicated above they may also occur in aged and debilitated persons. The toxicity of streptomycin is one of many reasons for utilizing the simplest effective antibiotic therapy.

The disadvantages of penicillin-streptomycin combinations also hold for penicillin-dihydrostreptomycin combinations, which are still being marketed despite the fact that dihydrostreptomycin can cause severe and irreversible deafness.

Finally, it should be noted that the use of fixed-ratio streptomycin-penicillin combinations is not only likely to be either unnecessary, ineffective or hazardous, but that it also tends to encourage the emergence, increase and spread of organisms resistant to penicillin and streptomycin.

COTAZYM

Though it is promoted as a "break-through in cystic fibrosis," Cotazym (Organon), a concentrated pancreatic enzyme preparation, has no effect on the fundamental defect in this disease, abnormal viscosity of bronchial and pancreatic secretions (mucoviscidosis), or on the fatal pulmonary lesion. Like other hog pancreas preparations which have long been available, however, it does provide replacement of lipase in the pancreatic enzyme deficiency characteristic of cystic fibrosis. It thus permits more nearly normal digestion of fats, relieving steatorrhea, diarrhea and flatulence, and improving the patient's nutrition and strength. The advantage of Cotazym over such pancreatin preparations as Viokase and Panteric is its greater acceptability; doses are smaller and the odor is less offensive, as is the odor of the urine, stool and flatus.

The only published clinical report on Cotazym is a study on 13 children with pancreatic cystic fibrosis (E. B. Best, et al., South. Med. J., 53:1091, 1960); a glyceryl trioleate test meal containing radioiodine was given to nine of the patients. Stool radioactivity fell markedly with a considerable rise in blood radioactivity in every instance when 300 mg. of Cotazym was added to the test meal. All 13 children gained in weight.

RELATIVE POTENCY - Despite the absence of published studies of the comparative potency of the different pancreatic enzyme preparations, the experience of investigators consulted by The Medical Letter leaves little doubt that Cotazym is effective in relatively small doses; weight for weight, its lipolytic activity appears to be at least three times that of any other pancreas preparation. This advantage can be an important one with children who refuse to take the necessarily large doses of the older products. No pancreatic extract is likely to be helpful in the steatorrhea of malabsorption associated with ileitis, bowel resections, tuberculosis, lymphomas, or in the post-gastrectomy state.

DOSAGE - The recommended starting dose of Cotazym is three 100-mg. capsules before each meal and one before each snack. It is sometimes possible to reduce the dose to two capsules before each meal. For children unable to swallow capsules, the contents can be spread on food. Since gastric acidity, gastric emptying time, and degree of alkalinization in the duodenum vary, some destruction of Cotazym is likely even when it is taken with food. If Cotazym is ineffective, enteric-coated pancreatic enzyme tablets should be tried. Enteric coating, however, often causes a preparation to pass through the intestines without being absorbed.

The absence of reliable figures for the relative potency of the different products makes it difficult to compare costs, but Cotazym appears to be considerably more expensive than other preparations. One hundred capsules (100 mg.) of Cotazym cost about $8 to $9.50; 100 five-grain (about 300 mg.) tablets of Viokase (Vio-Bin Corp.) cost about $4.50 to $5.50; 4 oz. (about 120 Gm.) of Viokase Powder costs about $8 to $10; 4 oz. of Panteric Granules (Parke, Davis) costs about $6.50 to $8; 100 enteric-coated five-grain Pancreatin Enseals (Lilly) cost about $4 to $5; Lilly's plain Pancreatin tablets cost about half as much. Less expensive pancreatin preparations offered by a number of smaller companies can be tried and continued if effective.

POLIOVIRUS VACCINES

The hope expressed last fall by the Surgeon General that the Sabin oral poliovirus vaccine would be marketed in the United States before the summer of 1961 is not being realized. There is some disagreement as to whether the pharmaceutical manufacturers are finding it difficult to meet the safety standards for commercial production set by the National Institutes of Health or whether, for their own reasons, they are simply not interested in pushing the production of the Sabin vaccine. In any event, it is unlikely that significant quantities of the vaccine will be available in the United States before 1962 at the earliest.

SALK VACCINE - The continued use of the Salk (killed-virus) vaccine should, therefore, be vigorously promoted by health agencies and by physicians, so that as many people as possible below the age of 50 will be protected by the full series of four injections. According to the U.S. Public Health Service, the incidence of paralytic polio is now highest among "babies and bread-winners" in low-income families — indicating where the greatest effort to encourage the use of the Salk vaccine is needed.

Public Health Service figures show that in the United States as a whole during the year 1959, paralytic polio was prevented in about 95 per cent of those who received four injections of Salk vaccine (J. Salk, Lancet, 2:715, 1960). The commercial salk vaccines are being steadily improved in potency and uniformity (Merck's Purivax is an example of such improved vaccine), and there is reason to hope for even better results this year. Notwithstanding controversy over the respective merits of live- and killed-virus vaccine, once the oral poliovirus vaccine becomes available it is likely that both vaccines will be used to eliminate poliomyelitis as a public-health problem.

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